


CASE REPORT

Heterogeneity-based, multiple mechanisms in the resistance to osimertinib (AZD9291): A case report

Yutao Liu¹, Xuezhi Hao¹, Xingsheng Hu¹, Junling Li¹, Yan Wang¹, Hongyu Wang¹, Puyuan Xing¹, Weihua Li², Jianming Ying², Xiaohong Han³ & Yuankai Shi¹ 

1 Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

2 Department of Pathology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

3 Department of Clinical Laboratory, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Keywords

Epidermal growth factor receptor T790 mutation; heterogeneity; MET amplification; osimertinib; resistance.

Correspondence

Yuankai Shi, Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, No.17 Panjiayuan Nanli, Chaoyang District, Beijing 100021, China.
Tel: +86 10 8778 8293
Fax: +86 10 8777 8740
Email: syuankai@cicams.ac.cn

Received: 21 November 2017;

Accepted: 18 December 2017.

doi: 10.1111/1759-7714.12596

Thoracic Cancer 9 (2018) 498–501

Abstract

Osimertinib is a novel, irreversible, mutant-selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor targeting EGFR mutations and the EGFR T790 mutation. Here, we report a woman with EGFR-mutated lung adenocarcinoma who, after 23-month treatment with gefitinib, developed the EGFR T790M mutation, which converted the T790M status from positive to negative before osimertinib treatment and developed MET amplification, leading to rapid progression on osimertinib in two months. Subsequent treatment with crizotinib and c-Met inhibitor plus gefitinib also failed to improve the clinical outcome, suggesting the potential existence of another resistance mechanism. Our findings revealed the underlying multiple and heterogeneous mechanisms in resistance to osimertinib, suggesting combination strategies should be considered post-osimertinib progression.

Introduction

Osimertinib (AZD9291) is a third-generation and mutation-selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) used in patients with EGFR T790M mutant non-small cell lung cancer (NSCLC) who failed prior treatment with EGFR TKIs.^{1–3} However, acquired resistance to osimertinib inevitably occurs. Here, we report multiple and heterogeneous mechanisms involved in the resistance to osimertinib, which induce rapid disease progression.

Case Report

The patient was a 63-year-old, never-smoker, Asian woman with stage IV lung adenocarcinoma harboring

EGFR Del19 mutation (by ARMS). She was treated with gefitinib for 23 months with partial response as the best response and progressed in October 2015. Re-biopsy of the lung found an EGFR Del19 mutation and an exon 20 T790M mutation by the PCR method using cobas[®] EGFR Mutation Test v2 assay (Roche Molecular Diagnostics, Pleasanton, CA, USA). The patient was then enrolled in the phase 3 study of AZD9291 (AURA 3) and assigned to the chemotherapy group (pemetrexed/cisplatin), achieving partial response after two-cycle treatment, and progressed after four-cycle chemotherapy and two-cycle pemetrexed maintenance. The EGFR Del19 mutation (ARMS) and c-Met amplification (FISH+ and IHC 2+) was detected, but not the T790M mutation. This patient was

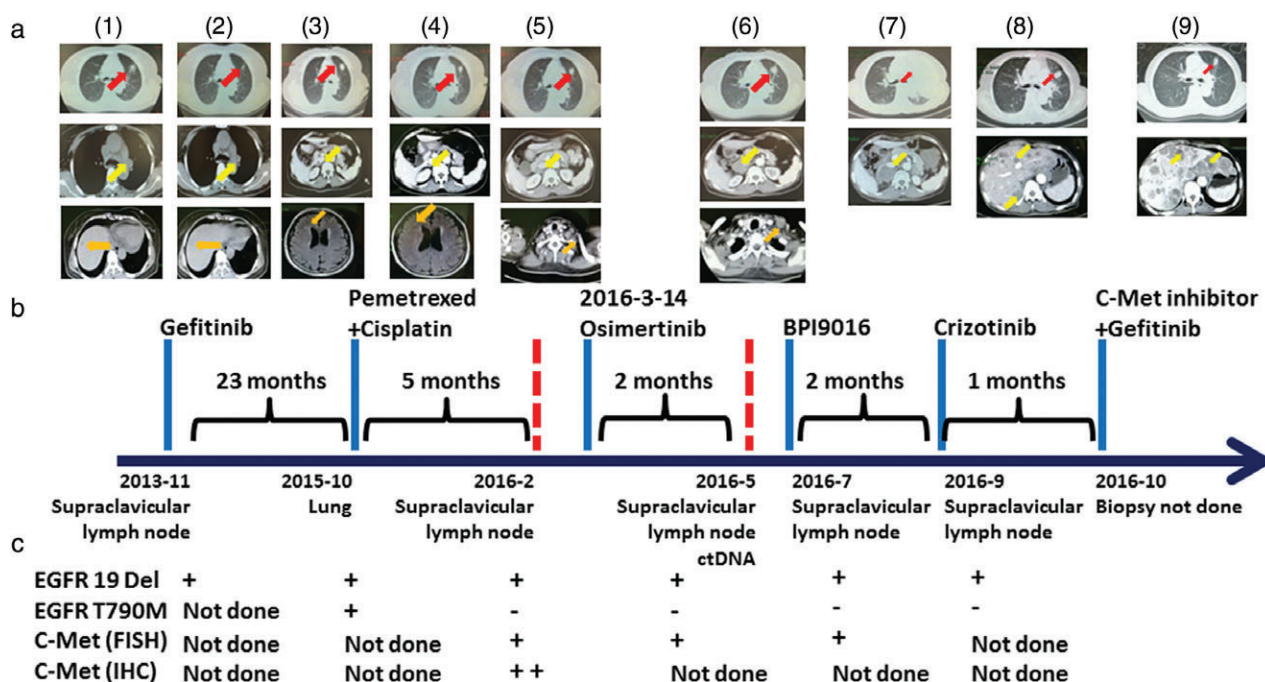


Figure 1 Patient clinical course including treatment history and relevant imaging studies and tumor biopsy specimens. (a) Representative images of computed tomography scan with different timings. (1) At baseline before gefitinib, showing left pulmonary lesion and liver metastasis. (2) At three months, with a partial tumor response. (3) At baseline before chemotherapy, with left pulmonary nodes, lymph node, and brain metastasis. (4) At two months, left pulmonary nodes, lymph node, and brain metastasis showing partial tumor response. (5) At baseline before osimertinib, with enlarged left pulmonary nodes and left supraclavicular lymph node metastasis. (6) At two months of treatment with osimertinib, lung and left supraclavicular lymph node tumor progression. (7) At two months of treatment with BPI9016, progressed disease with pleural effusion. (8) At one month crizotinib treatment, with stable disease in the lung and multiple metastases in the liver. (9) At one month of treatment with a novel c-Met inhibitor plus gefitinib, with stable disease in the lung and multiple metastases in the liver. (b) Patient clinical course between 2013 and 2016. (c) Sample analysis readings from sequential tumor biopsy specimens (pre-gefitinib, pre-chemotherapy, pre- and post-osimertinib).

then crossed over to receive osimertinib 80 mg once daily according to the AURA 3 protocol, and rapidly progressed in two months with progressed disease as the best tumor response, while shrinkage of the intracranial tumor was seen. Liquid molecular analysis by PCR showed an activating EGFR Del19 mutation, but no EGFR T790M or C797S mutation, while c-Met amplification was found in a tumor biopsy of the supraclavicular lymph nodes. The patient was then enrolled in a clinical trial evaluating a new c-Met inhibitor, BPI-9016, in June 2016, and achieved stable disease; however, the duration of the clinical benefit only lasted for three months. Post-progression next-generation sequencing results revealed the EGFR Del19 mutation without any signal of other biomarkers (including KRAS, NRAS, BRAF, PIK3CA, HER-2, RET, PDGFRA, and C-KIT). Crizotinib plus gefitinib was suggested; however, concerned about the potential toxicity, she started single-agent crizotinib, and continued to receive a c-Met inhibitor plus gefitinib after progression on crizotinib. During these treatments, the tumor in the lung was well controlled, while significant progress was seen in the liver. The patient died in December 2016 (Fig 1).

Discussion

Osimertinib (AZD9291) is a mutant-selective, third-generation EGFR TKI that is designed to overcome the acquired T790M-mediated TKI resistance. In the phase 1 component of AURA, osimertinib demonstrated an objective response rate of 61% and a progression-free survival was 9.6 months in patients with T790M-positive NSCLC.¹ A pooled analysis of two subsequent phase 2 studies of osimertinib further confirmed these findings, the overall response rate was 66% and the median progression-free survival was 11.0 months in 411 T790M-positive NSCLC patients.² More recently, the phase 3 AURA 3 study found that patients with T790M-positive NSCLC who were treated with osimertinib had a better overall response rate and longer progression-free survival than did those receiving chemotherapy after first-line therapy with EGFR TKI.³ Furthermore, the benefit of osimertinib was also shown in patients with central nervous system metastases by a longer duration of progression-free survival.³ Based on these studies, osimertinib is recommended as standard therapy for patients with metastatic EGFR T790M mutation-positive NSCLC, who have progressed on or after EGFR-TKI

therapy. However, like early-generation EGFR TKIs, development of clinical resistance to osimertinib has also been reported. So far, several mechanisms of resistance have been identified in osimertinib and other third-generation EGFR TKIs, including acquired EGFR C797S mutation, loss of EGFR T790M mutant clones, activation of bypass pathway, and histological transformation.^{4–9}

In this case, we identified an activating T790M mutation at the time of acquired resistance to gefitinib; however, after chemotherapy, the wild-type T790 became the dominant driver of tumor growth. The main explanation is the coexistence of positive T790M and wild-type T790 clones before osimertinib treatment. The true biopsy of a T790M “positive” tumor is more than a binary positive/negative variable. The coexistence of positive and wild-type T790 clones within a tumor makes osimertinib suppress the growth of T790-positive cells, while the T790 wild-type clones escape and mediate the development of resistance.⁸ Furthermore, the degree of this heterogeneity is predictive of response: a tumor with a higher fraction of T790M-positive cells at baseline is associated with a better response to third-generation EGFR TKIs.⁸ In addition, chemotherapy may affect the EGFR mutation status in tumor cells due to the different sensitivities of EGFR-mutated and wild-type tumor cells to chemotherapy; it is possible that similar a mechanism exists in EGFR T790-positive tumor cells.¹⁰ Alternative pathway activation, MET amplification, was also identified in our case. However, heterogeneous responses were noted after single c-Met inhibitor or combination of c-Met inhibitor and EGFR TKI, while no other biomarkers were found. These findings indicated the potential existence of multiple mechanisms of resistance within a tumor, such as histological transformation to small cell carcinoma.⁶ Last but not least, the heterogeneity of biopsy status between primary and metastatic tumor lesions should also be noted.¹¹ In this case, although the biopsy was conducted in the lung and in the lymph nodes pre- and post-chemotherapy, respectively, the rapid overall treatment failure to osimertinib suggested that the T790M mutation status in the lymph nodes was consistent with that in the lung.

Increasing attention has been paid to the application of plasma genotyping. A lack of available tissue for molecular assessment is commonly seen in real-world practice; single-site biopsies might not be representative of the overall predominant resistance mechanisms due to the heterogeneity of metastases^{12,13} furthermore, liquid biopsy has potential applications for dynamic monitoring of the efficacy of targeted therapies and early detection of resistance mutations.^{14–16} Oxnard *et al.* reported that an equivalent outcome was seen in patients with positive T790M in plasma to those with positive T790M in tissue, supporting the use of plasma genotyping.¹⁷ In the current study, liquid

biopsy was used once as surrogate samples after progression on multiple-line treatments, the lack of temporal monitoring of the EGFR T790M by plasmatic test is a major limitation of this report.

Our findings provide evidence for the coexistence of multiple mechanisms in the resistance to osimertinib within a tumor; furthermore, the resistance mechanism may vary between tumor lesions in one patient. Currently, combination trials of osimertinib and other pathway inhibitors are being investigated (TATTON, NCT02143466). This report further supports the combined regimens of T790-targeted agents and other drugs to target T790-wild-type cells or other bypass pathway when making clinic decision.

Acknowledgment

This study was funded by the Chinese National Project for New Drug Innovation (2017ZX09304015).

Disclosure

No authors report any conflict of interest.

References

- Jänne PA, Yang JC-H, Kim D-W *et al.* AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* 2015; **372**: 1689–99.
- Yang J, Ramalingam SS, Jänne PA, Cantarini M, Mitsudomi T. LBA2_PR: Osimertinib (AZD9291) in pre-treated pts with T790M-positive advanced NSCLC: Updated Phase 1 (P1) and pooled Phase 2 (P2) results. *J Thorac Oncol* 2016; **11** (Suppl): S152–3.
- Mok TS, YL W, Ahn MJ *et al.* Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* 2017; **376**: 629–40.
- Yu HA, Tian SK, Drilon AE *et al.* Acquired resistance of EGFR-mutant lungcancer to a T790M-specific EGFR inhibitor: Emergence of a third mutation (C797S) in the EGFR tyrosine kinase domain. *JAMA Oncol* 2015; **1**: 982–4.
- Thress KS, Paweletz CP, Felip E *et al.* Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. *Nat Med* 2015; **21**: 560–2.
- Kim TM, Song A, Kim DW *et al.* Mechanisms of acquired resistance to AZD9291: a mutation-selective, irreversible EGFR inhibitor. *J Thorac Oncol* 2015; **10**: 1736–44.
- Ortiz-Cuaran S, Scheffler M, Plenker D *et al.* Heterogeneous mechanisms of primary and acquired resistance to third-generation EGFR inhibitors. *Clin Cancer Res* 2016; **22**: 4837–47.
- Piotrowska Z, Niederst MJ, Karlovich CA *et al.* Heterogeneity underlies the emergence of EGFR T790 wild-

- type clones following treatment of T790m-positive cancers with a third-generation EGFR inhibitor. *Cancer Discov* 2015; **5**: 713–22.
- 9 Ou SH, Agarwal N, Ali SM. High MET amplification level as a resistance mechanism to osimertinib (AZD9291) in a patient that symptomatically responded to crizotinib treatment post-osimertinib progression. *Lung Cancer* 2016; **98**: 59–61.
- 10 Bai H, Wang Z, Chen K *et al.* Influence of chemotherapy on EGFR mutation status among patients with non-small-cell lung cancer. *J Clin Oncol* 2012; **30**: 3077–83.
- 11 Chen ZY, Zhong WZ, Zhang XC *et al.* EGFR mutation heterogeneity and the mixed response to EGFR tyrosine kinase inhibitors of lung adenocarcinomas. *Oncologist* 2012; **17**: 978–85.
- 12 Remon J, Faivre L, Facchinetti F *et al.* Radiogenomics in 332 metastatic non-small cell lung cancer (NSCLC) patients. *J Clin Oncol* 2015; **15** (Suppl): 11563–3.
- 13 Piotrowska Z, Nierdest MJ, Mino-Kenudson M *et al.* Variation in mechanisms of acquired resistance among EGFR-mutant NSCLC patients with more than 1 postresistance biopsy. *Int. J Radiat Oncol* 2014; **90**: S6–7.
- 14 Marchetti A, Palma JF, Felicioni L *et al.* Early prediction of response to tyrosine kinase inhibitors by quantification of EGFR mutations in plasma of NSCLC patients. *J Thorac Oncol* 2015; **10**: 1437–43.
- 15 Mok T, Wu YL, Lee JS *et al.* Detection and dynamic changes of EGFR mutations from circulating tumor DNA as a predictor of survival outcomes in NSCLC patients treated with first-line intercalated erlotinib and chemotherapy. *Clin Cancer Res* 2015; **21**: 3196–203.
- 16 Sorensen BS, Wu L, Wei W *et al.* Monitoring of epidermal growth factor receptor tyrosine kinase inhibitor-sensitizing and resistance mutations in the plasma DNA of patients with advanced non-small-cell lung cancer during treatment with erlotinib. *Cancer* 2014; **120**: 3896–901.
- 17 Oxnard GR, Thress KS, Alden RS *et al.* Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced none-small cell lung cancer. *J Clin Oncol* 2016; **34**: 3375–82.